

Alithiasic cholecystopathies – from medical treatment to scalpel

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Abstract. Introduction Alithiasic cholecystopathies are common and costly. Many risk factors for gallbladder pathology are not modifiable, such as ethnic background, increasing age, female gender, pregnancy, and family history or genetics. Conversely, the modifiable risks for gallbladder diseases are obesity, rapid weight loss, total parenteral nutrition or fasting, and a sedentary lifestyle. The rising epidemic of obesity and metabolic syndrome predicts an escalation of gallbladder dysfunction and gallstone frequency. **Discussions** A number of the described clinical manifestations are common to other diseases of the digestive tract or of the accessory glands, requiring a detailed differential diagnosis and, respectively, a lesion assessment to make the correct therapeutic decisions. Ultrasonography is the best epidemiological screening method to accurately determine the point prevalence of gallbladder calculi and alithiasic cholecystopathy. A thorough evaluation of acalculous chronic cholecystitis is crucial for making the right therapeutic decisions. Considering the previously stated elements, we propose the following therapeutic attitude: a) alithiasic vesicular disease with a firm surgical indication: gallbladder suspicion of neoplasia, limy bile, gallbladder adenomyomatosis, vesicular trauma, malformations, volvulus, and acute cholecystitis; b) alithiasic cholecystopathies of a medical nature: biliary dyskinesias (hypo and hypertonic), cholesterolosis, chronic alithiasic cholecystitis, cystitis with secondary vesical pain, evacuation disorders in the conditions of an Oddi's sphincter contraction. **Conclusion** The effectiveness of conservative treatment is assessed based on clinical imaging criteria and therapeutic tests. In contrast, for certain well-defined entities, the treatment is surgical (e.g., failure of conservative treatment, neoplasia, adenomyomatosis).

Keywords: ALITHIASIC CHOLECYSTOPATHIES, CHOLECYSTECTOMY, GALLBLADDER POLYPS, GALLBLADDER CANCER

INTRODUCTION

Understanding the optimal functionality of any organ, apparatus, or system is complex, as it relies on the typical structure and numerous elements that constitute appropriate physiology. Human pathology, and pathology in general, has identified many situations in which structural elements are missing or defective (congenital or acquired) or various functional components are in a temporary or definitive limitation of the optimal physiological parameters. However, we

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frequently find structural alterations or functional defects on multiple levels, such as pancreatic insufficiency, that do not significantly affect the 'morpho-functional unit' we refer to. Well-defined pathological typologies generally benefit from explicit therapeutic schemes (if they exist), while imprecisely delimited affections (probably for semantic reasons) represent experiments, hypotheses, and sometimes speculations [1].

Throughout history, we have witnessed the dynamic nature of medical knowledge, with firm, inflexible approaches and theories that later lost their relevance, became contradictory, or even prohibited. This constant evolution is what keeps our field exciting and full of potential. It is the natural evolution of attempts to optimize solutions for various problems related to human health. Other times, reconsidered and improved abandoned theories represent the basis of analysis for further studies [2,3,4]. Complex and elaborate therapeutic trials are sometimes disappointing, while treatment solutions without great initial hopes determine new prospects with chances of success. The forms of treatment (medical or surgical) initially full of hope did not receive validation in time, and variants that were less ambitious or successful at the beginning later entered the basic long-term therapeutic schemes.

At the same time, the established therapeutic schemes (with their derivative variants), which have confirmed their firm efficacy, will likely not be able to be replaced, constituting mandatory and definitive therapeutic measures. However, the emergence of new variants or therapeutic solutions, such as minimally invasive surgeries or targeted drug therapies, may offer a new evolutionary perspective for finding superior results in treating various diseases. The treatment of cholecystopathy is a complex puzzle, with drug treatment algorithms aiming to navigate the delicate balance between adverse effects and positive outcomes. This intricate process requires careful consideration of each patient's unique circumstances, with the potential to amplify or even potentiate positive effects.

Medical professionals face unique challenges in treating mixed diseases (medical-surgical). The objectives are to limit operative

risks and maximize the benefits of the operative treatment through a rigorous surgical tactic and technique tailored to the respective case. A significant challenge is the precise delineation of the limit to which medical treatment is valuable and sufficient and where surgical intervention is necessary. This is particularly relevant in the case of cholecystopathies that do not fall within exclusive surgical competence.

CHOLECYSTOPATHY – THE "APPENDICITIS" OF ADULT AND ELDERLY PATIENT

If, during childhood and at a young age, appendicitis represents the main health problem with surgical connotations, biliary disorders occupy the first place in middle-aged adults and seniors, followed by neoplasms of the digestive tract and parietal defects. Gallbladder lithiasis and its complications are the most frequent and well-defined clinical entity with a firm or absolute surgical indication. Other diseases require surgical intervention (gallbladder neoplasms, acute alithiasic cholecystitis, or diseases unresponsive to conservative treatment). The accumulation of factors impacting the biliary tract (anatomical, dietary, age, infectious, metabolic, vascular, traumatic) can induce various types of biliary-type suffering, or with the additional involvement of the gallbladder and common bile duct, in a more complex digestive context [5-8]. The complicated symptomatology that results in these conditions can make it challenging to assess biliary suffering and establish the optimal therapeutic strategy. The causes and mechanisms involved in the genesis of biliary tract lesions are highly diverse and can have a direct or indirect effect [9]. The main incriminated elements are:

- congenital malformations with consequences on the dynamics of the biliary tract;
- neurohormonal disorders that influence the motility of the biliary tract, with functional dyssynergies;
- dyscholia, due to the imbalance between the bile components, favors the appearance of cholesterol achenes and changes in the gallbladder wall;

- repetitive symptomatic or subclinical inflammatory episodes with the induction of biliary epithelial changes and functional consequences;

- pancreatic or duodenal-pancreatic reflux in the bile ducts that can generate biliary tract dysfunction, with clinically confusing and difficult-to-treat consequences;

- sclerosing cholangitis plus other autoimmune factors;

- humoral factors (cholecystokinin);

- intravesicular hyper-pressure that can develop intramural diverticulosis (Rokitansky-Aschoff sinuses);

- disorders of the contractility of the vesicular walls in excess or deficit;

- alteration of the vesicular resorption process;

- intravesicular stasis due to cystic permeability disorders, inflammatory adenopathies (tumors, lymphatic blockages), Lutkens sphincter hypertonia, Mirizzi Syndrom;

- recurrent bile infections in various pathological context;

- vagotomy or sympathetic hypertonia;

- neuropsychic disorders;

- various hormonal disorders;

- other factors include gastric or duodenal ulcers, infections with hepatitis viruses, gastroesophageal reflux, and even diseases of the genital tract or collagenosis.

The factors mentioned above can affect the structure of the gallbladder wall (parietal thickening through an inflammatory process, appearance of cholesterol achenes, intramural diverticulosis, cystic sclerosis, adenomyomatosis, or metaplasia of the unstratified squamous epithelium). However, no significant changes are sometimes found on the surgical/necropsy pieces (without vesicular lithiasis).

Purely functional disorders of the gallbladder (hypertonic biliary dyskinesias, hypotonic biliary, up to Chiray-Pavel gallbladder atonia) do not present a histopathological substrate if no other pathogenic elements occur on the biliary tract.

The previously mentioned multi-vector pathogenesis most frequently generates the appearance of gallstones. However, there are situations in which the possible pathogenic archetype with phylogenetic determinism remains that of lithiasis cholecystopathy. The severity of the resulting clinical manifestations is difficult to quantify, and the patient's sensitivity threshold and the grading of sufferance induced by the psychological factor can be confusing when making a therapeutic decision. The heterogeneity of the entities that make up the pathological complex generically called "alithiasic cholecystopathy" sometimes makes it difficult to fit it precisely into one of the specific typologies to guide the appropriate treatment.

Over time, insufficiently standardized terminology, hesitant or insufficiently outlined classifications, and sometimes unclear physiopathology have generated inefficiency or erroneous therapeutic decisions. Administering a long-term medical treatment with questionable efficiency or early cholecystectomy without exhausting non-operative treatment solutions are both therapeutic mistakes to avoid [10]. A significant arsenal of paraclinical and laboratory investigations is available for investigating the biliary tree. A series of biological parameters relevant to the suffering of the biliary tract: blood count, liver cytolysis tests, bilirubinemia (with its components), intrahepatic cholestasis parameters, and serum protein electrophoresis have crucial diagnostic value.

Plain abdominal X-ray, ultrasonography, oral cholecystography, intravenous cholecystocholangiography (increasingly rarely used), biliary scintigraphy with technetium, computer tomography, transparietohepatic cholangiography, magnetic resonance imaging, retrograde endoscopic cholangiopancreatography, and echo-endoscopy may bring essential benefit for diagnostic [11]. The information these investigations provide is precious and detailed from a morphological point of view. Still, it is poorer from a functional point of view (except for oral cholecystography with Boyden lunch and later x-ray exposure, duodenal biliary drainage, and intravenous cholecysto-

cholangiography) [12]. Consequently, these investigations highlight the gallbladder lesions in detail. Essential functional elements missing from modern imaging techniques must be highlighted following a patient's medical history, clinical imaging, and biological evaluation to enable accurate diagnosis.

Considering the clinical polymorphism and the difficulties of semantic framing of non-lithiasis gall bladder lesions, we have framed these distinct entities as follows:

a) alithiasic cholecystopathies where imaging exams cannot detect a morphological substrate at the level of the gallbladder wall; this category includes the whole range of dystonia/dyssynergy and vesicular dyskinesia, which results from the desynchronization of vesicular dynamics about sphincter activity, the permeability of the evacuating channels, the state of the CBP, and the efficiency of bile evacuation in the digestive tract. This complex activity is neuronal reflex-mediated (the vagus nerve modulates the VB contraction and the splanchnic activity of the sphincters of Lutkens and Oddi) and humoral (cholecystokinin), followed by food intake. We deduce from these aspects that there may be vesicular dysfunctions with clinical expression, the causes of which are at the bile duct or sphincter level. It results in a mosaic of functional disorders of the gallbladder or extrahepatic biliary tree, the gallbladder being only their clinical resonator.

b) alithiasic cholecystopathies in which we can identify a morphological substrate (form, structure, or content). In the second category, we record a multitude of biliary congenital changes of the gallbladder (changes in shape, topographical anomalies, vesicular or cystic aplasia) or more frequently acquired (volvulus of the gallbladder, vesicular calcareous cholesterolosis, adenomyomatosis, diverticulosis and of the gallbladder). Although rare, congenital cholecystopathies include a multitude of manifestations of the shape or topography of the gallbladder or cystic duct with different clinical consequences. They are generally diagnosed early but can remain silent, being discovered intraoperatively or at autopsy.

Abnormalities of the length, caliber, and trajectory of the cystic duct and abnormalities of the shape of the gallbladder (double bladder, plied, biloculated, or hourglass) are not uncommon. The mobile gallbladder (very long gallbladder mesothelium) is in an atypical position. The particular way of discharging the gallbladder is due to abnormalities of the cystic duct (low-level discharge to the common bile duct of the cystic duct, or cystic duct "in the swan's neck," or with spiral discharge). Sometimes, accessory hepatic ducts (additional segmental duct, double accessory duct) open directly in the gallbladder. At other times, congenital anomalies of the CBP are identified, with possible implications for gallbladder functions (segmental choledochal dilatations, congenital mega choledochoce, Alonso-Lej's choledochoce).

Acquired alithiasic chronic cholecystopathies are more frequent and usually have gallbladder wall changes, including or not a chronic inflammatory process. These parietal changes favor lithogenesis but may remain evolutionary in an alithiasic stage. Among them, cholecystosis represents a heterogeneous group of vesicular diseases involving different parietal changes. The absence of inflammation is a common characteristic. The main entities are:

- vesicular lipoidosis (strawberry gallbladder) or cholesterolosis is characterized by accumulations in the chorion and under the mucosa of histiocytic cells loaded with crystalline cholesterol compounds (fig. 1);



Figure 1. Strawberry gallbladder (cholesterolosis blue arrow)

- vesicular calcinosis (porcelain vesicle) involves infiltrating the vesicular wall with fibrous tissue loaded with calcareous deposits [13];

- limy bile syndrome: contains a white paste of calcium carbonate that does not deposit in the walls but fills the gallbladder (obstructed cyst) [14]. Direct images of the diffusely opacified gallbladder without the precisely delimited border of the porcelain bladder;

- alithiasic scleroatrophic gallbladder;

- adenomyomatosis, which is characterized by the accumulation of parietal nodules located predominantly in the infundibulo-cystic region, going up to the pseudotumoral appearance. (Fig. 2-4);

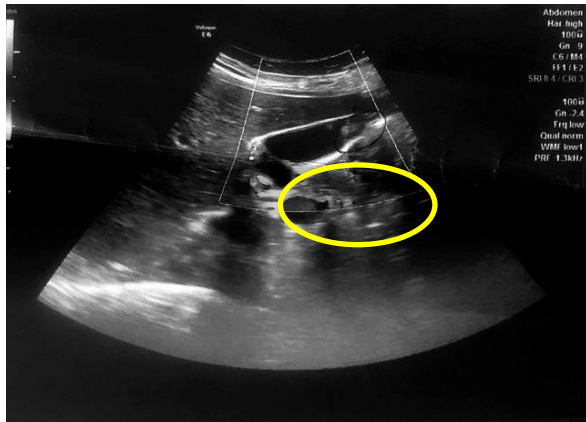


Figure 2. Adenomatosis of the gallbladder wall (yellow mark) – ultrasound exam

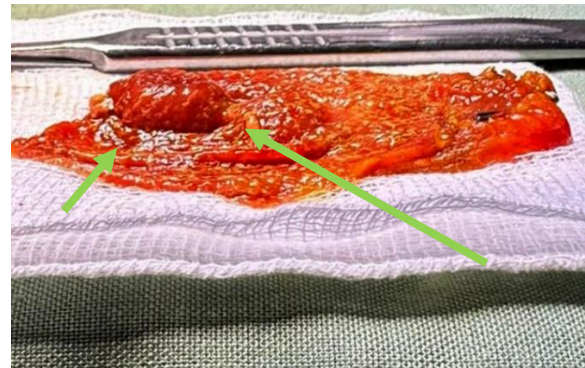


Figure 4. Adenomatosis of the gallbladder wall (green arrows) – postoperative sectional exam

- gallbladder diverticulum/parietal diverticulosis (Rokitansky-Aschoff sinuses), which can also be congenital (Fig.5-6);



Figure 5. Gallbladder diverticulum – ultrasound finding (yellow arrow)

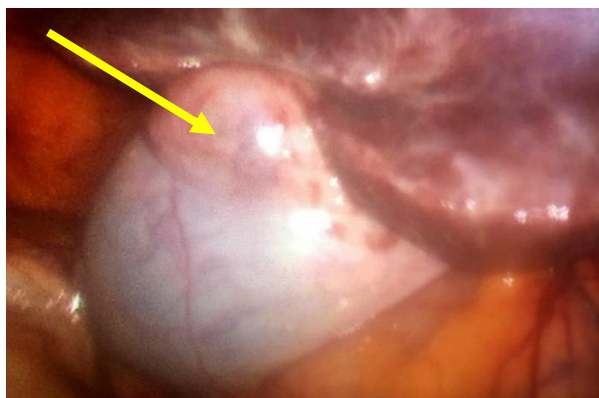


Figure 3. Adenomatosis of the gallbladder wall (yellow arrow) – intraoperative print screen

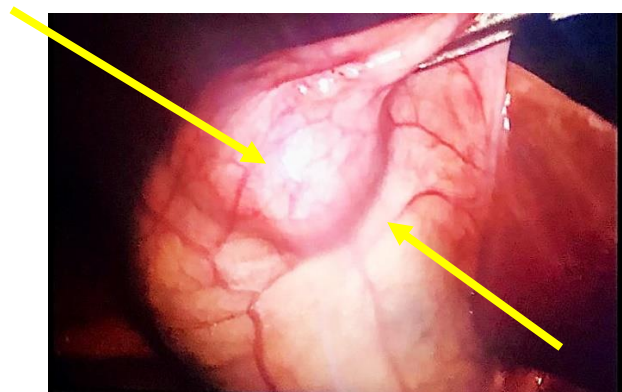


Figure 6. Gallbladder diverticulum – same patient as above, intraoperative printscreen (yellow arrows)

- gallbladder polyp;
- gallbladder papillomatosis: mucosa-associated vegetation with hyperplasia of the muscular structure. It can be confused with adenomyomatosis or vesicular tumors (cholecystitis glandularis proliferans).

In some of these entities, we can find gallbladder evacuation disorders (Oddi's or cystic duct inflammation): cystic duct syndrome, or alithiasic chronic cholecystitis arising from episodes of repetitive acute cholecystitis, hydatid liver disease, vascular disorders, collagenosis, or parasitic infections. It can host variable amounts of sludge that can hide microcalcifications. Isolated cystic duct inflammation is possible, but it is usually associated with inflammation of the gallbladder wall met in gallbladder injuries, benign tumors, adenomyoma, papilloma, and lipoma. Malignant tumors are closely related to the coexistence of gallstones.

DISCUSSIONS

Alithiasic cholecystopathies, a group of diseases with significant frequency and diagnostic challenges, continue to pose a health concern despite their lack of severe symptoms or serious evolutionary potential in most cases. Located on the border between the field of medical conditions and those with surgical therapeutic solutions, alithiasic cholecystopathies (ALC) were frequently diagnosed or evaluated incorrectly with sometimes erroneous therapeutic consequences. The extremes of this situation have ranged from exaggerated and irrational food regimens and drug treatment schemes, to early and abusive cholecystectomies (and other types of interventions in the hepatobiliary sphere), sometimes resulting in unfavorable postoperative results and frequent complications.

The symptomatology of the acalculous chronic cholecystitis is polymorphic and uncharacteristic, being dominated by pain/discomfort in the right hypochondrium and epigastrium accompanied by migraine, nausea and vomiting, bloating, and intolerance to cholecystokinetic foods. Intestinal gurgling, transit disorders, neurovegetative manifestations, and weight loss may occur as a result of avoiding

food consumption for fear of postprandial digestive disorders. A mild level of jaundice (when it happens) is temporary, appears after colic and disappears spontaneously or after antispasmodic medication, and due to the mobilization of cholesterol crystals through the duodenal papilla or prolonged Oddi` sphincter spasms. Noisier manifestations are found in vesicular hypertension (with or without associated cystitis) when we see frequent biliary colic, severe food intolerance, bilious vomiting, and epigastric pain. Oddi's hypertension (independent or related to vesicular disorders) can take on purely painful or icteric forms, mimicking choledochal lithiasis.

A number of the clinical manifestations described are common to other diseases of the digestive tract or the accessory glands (although they have particularities that can differentiate them), requiring a detailed differential diagnosis and, respectively, a lesion assessment to make the correct therapeutic decisions. Subjective anamnestic data (sometimes with neurotic accents and cenesthopathy), which usually follow a long-term disorder, must be considered because it can precipitate incorrect treatment decisions.

Preserving an organ and its function (even partially preserved) is an objective that must always be in mind. So, there are today repeated attempts to optimize the variants of conservative, medicinal treatment associated with hygiene-dietetic measures that succeed in a significant number of cases in obtaining consistent improvements in symptoms with good clinical comfort. The drug arsenal with hepatobiliary tropism has improved and diversified significantly, currently benefiting from a varied range of antibiotics, antispasmodics, cholecystokinetics, hepatoprotective, prokinetics, and enzyme supplements, but also from numerous placebo preparations, or without notable therapeutic benefits. Other therapeutic solutions were also associated, such as duodenal drainage (Meltzer-Lyon test) and adapted hydromineral spa treatments.

Today, the morphological details of the biliary tract are easy to obtain considering the varied range of targeted investigations, which can select cases with clear surgical indications (vesicular tumors, porcelain gallbladder, calcium gall bladder, adenomyomatosis, or vesicular papillomatosis). Physiological elements of the biliary tract (in the case of the gallbladder) are more difficult to evaluate than the result of indirect, cumulative information. Investigations of the upper digestive tract, such as the esogastro-duodenal barium meal: gastric hyperkinesia (Barclay's sign), and duodenal stasis (Holzknecht's sign), currently abandoned, offer indirect information about the functionality of the biliary tree.

Currently, oral cholecystography or intravenous cholecysto-cholangiography is considered to be of historical interest and does not enter the imaging diagnostic algorithm. Also, the patients did not readily accept duodenal drainage (Meltzer-Lyon test) and timed duodenal intubation (which highlighted the lack of bile and established the "lithogenic index"). Conversely, these tests are relatively scarce in offering new information [15,16,17]. Tc99 HIDA scintigraphy is a valuable but difficult-to-access investigation that has yet to enter the current diagnostic arsenal. CT examination/ MRI cholangiography is superior in terms of morphological information [18].

Stemming from this imperative necessity, we used a current, cheap, and non-invasive investigation to which we tried to add a functional value, which we called "Boyden ultrasonography" or serial dynamic ultrasonography. It is about a standard ultrasound (on an empty stomach) in which we note the main morphological elements (including the size of the gallbladder), followed by a Boyden lunch (egg yolk, cream, or chocolate) and ultrasound re-examination at 30 minutes and 60 minutes (serial dynamic ultrasound), with the calculation of volumetric indices and estimation of the bile ejection fraction. It is helpful to demonstrate the inability of vesicular contraction (evacuation). Plain ultrasound is less efficient than 3D or 4D

ultrasonography but far more accessible. 3D and 4D ultrasound exams before and after fatty foods oral intake may show disturbances in gallbladder bile output due to the ability to detect changes in gallbladder volume before and after the meal, providing quantitative data on bile ejection fraction.

For cases with gallbladder hypertension, dynamic ultrasonography (DUS) uses a significant antispasmodic preparation to assess the relaxation of the pathologically contracted gallbladder [17]. Without the performance and diagnostic value of the cardiac ultrasound, the serial dynamic hepatobiliary ultrasound provides valuable information on the vesicular kinetics comparable to that of the musculotendinous examination. Periodic re-examination following the medication with biliary tropism permits the evaluation of the effectiveness of the administered treatment. A limitation of the method is the lack of information on the activity of the sphincter of Oddi, but can we try to sensitize the technique by using substances that act at this level (morphine derivatives or amyl nitrite).

Gallbladder kinetics turmoil, as well as the functionality of the Oddi sphincter, may also be present in the framework of some systemic disturbances or in the case of nonbiliary disorders (gastric or duodenal ulcer, neighborhood colic, or biliodigestive fistulas), which can influence the activity of the biliary tract. Diagnosing such disturbances is mandatory to avoid therapeutic errors.

The functionality of the sphincter of Oddi can affect the common bile duct, the pancreas, and the gallbladder. Prolonged spasms or organic stenoses can generate retrograde stasis, hypertension, contractility disorders, lithogenesis, and infections, which can induce structural changes with secondary functional consequences. Chronic diseases can evolve into acute ones, and surgical indications become prevalent. Thus, we can appreciate that the intra- and extrahepatic biliary morpho-functional unit can be influenced at any level by various factors that induce persistent and rebellious vesicular

dysfunction in hygienic and dietary treatment solutions.

The most comprehensive evaluation of treatment solutions in acalculous chronic cholecystitis must consider clinical criteria, paraclinical and laboratory investigations, morphological and dynamic factors, the elimination of associated conditions that can impact the hepatobiliary tract, the consistent application of a hygienic and dietary standard, and the effectiveness of medicinal therapeutic tests. This thorough evaluation is crucial for making the right therapeutic decisions. Considering the previously stated elements, we propose the following therapeutic attitude:

a) alithiasic vesicular disease with a firm surgical indication: limy bile, gallbladder adenomyomatosis, vesicular trauma, malformations, volvulus, acute alithiasic cholecystitis gallbladder, and gallbladder neoplasia [19]. According to GLOBOCAN 2018 data, gallbladder cancer is the 22nd in frequency but the 17th most fatal cancer worldwide. Early diagnosis is essential for improving survival, but unfortunately, gallbladder cancer does not have specific symptoms in the early stages [18,20-22].

b) alithiasic cholecystopathies of a medical nature: biliary dyskinesias (hypo and hypertonic), cholesterolosis, chronic alithiasic cholecystitis, cystitis with secondary vesical pain, evacuation disorders in the conditions of an Oddi's sphincter contraction. These patients receive a standardized hygienic diet regimen, medication with adequate biliary tropism, and elimination of associated factors (neurohormonal, psychological). The monitored parameters are the frequency of biliary colic or other associated manifestations (bloating, nausea, intestinal gurgling). Digestive tolerance is an essential criterion to avoid malnutrition with objective support or psychological connotations that can lead to food phobia. The reluctance for an early surgical procedure relies on the principle regarding the preservation of the organs and their function (optimization of the outstanding gallbladder function) as well as the possible "post-cholecystectomy syndrome," when the absence of the gallbladder generates polymorphic

suffering that is difficult to treat. The proposed scheme is the following:

- the improvement within six months of the clinical manifestations, under the conditions of a satisfactory diet (balanced and nutritionally sufficient), compliance with the other hygienic-dietary indications, and the correctly administered medication, indicates the effectiveness of the medical treatment and justifies its continuation if the patient appreciates the clinical comfort obtained;

- the lack of complete response/significant improvement or the impossibility of complying with the recommendations (work schedule, socio-economic problems) indicates the usefulness of surgical intervention after six months of conservative treatment.

CONCLUSIONS

1. Acalculous chronic cholecystitis represents a polymorphic group of gallbladder disorders with mutual implications on the common bile duct and the sphincter of Oddi.

2. The etiology is varied and sometimes obscure, and the symptomatology is polymorphic.

3. 3D and 4D ultrasonography represent significant advancements in the imaging and functional assessment of the biliary tract. When combined with functional testing, such as ultrasound exams after fatty food intake, these techniques enhance the ability to detect abnormalities, assess gallbladder functionality, and plan appropriate treatment strategies.

4. The effectiveness of conservative treatment is assessed based on clinical, imaging criteria and therapeutic tests.

5. The treatment is surgical in certain well-defined entities (e.g., failure of conservative treatment, neoplasia, adenomyomatosis).

6. The only solution for improving survival in any imaging suspicion of gallbladder neoplasia is early cholecystectomy.

CONFLICT OF INTEREST AND FUNDING

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